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SUPPLEMENTARY INFORMATION

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Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes

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Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes

SUPPLEMENTARY INFORMATION

Supplementary Excel Table guide, supplied as individual files

Supplementary Table 1. Breast cancer risk regions identified through genome-wide association studies.

(a) Definition of fine-mapping regions based on previous results. 179 variants across 152 genomic regions. Variants located less than 500kb away from each other were included in the same region. (b) Imputation quality metrics across the 152 fine-mapping regions.

Supplementary Table 2. Breast cancer risk signals and credible candidate variants (CCVs).

(a) Multinomial Logistic Regression models. (b) Strong signals (BCAC and CIMBA) multinomial logistic regression models. (c) Candidate causal variants and high posterior probability variants.

Multinomial logistic regression summary statistics X^2 p-value, estimated using 67,136 ER-positive and 17,506 ER-negative cases, together with 88,937 controls

Supplementary Table 3. Bio-features enrichment.

Logistic regression robust variance estimation for clustered observations, Wald test X^2 p-values estimated using 67,136 ER-positive and 17,506 ER-negative cases, together with 88,937 controls.

Supplementary Table 4. Consensus transcription factor binding motif enrichment.

(a) Transcription Factor consensus binding motif enrichment analysis. (b) Transcription Factor enrichment at MCF-7 H3K4me1 regions. (c) ER-positive CCVs overlap with transcription factor binding motifs significantly enriched

Logistic regression, Wald test X^2 p-values estimated using 67,136 ER-positive and 17,506 ER-negative cases, together with 88,937 controls.

Supplementary Table 5. Coding, splicing CCVs and overlap of CCVs with variant drivers of local gene expression.

(a) CCVs collocating with eQTL variants in normal breast tissue. (b) CCVs collocating with eQTL variants in breast tumor tissue. (c) CCVs coding annotation. (d) CCVs predicted to affect splicing

Logistic regression robust variance estimation for clustered observations, Wald test X^2 p-values estimated using 67,136 ER-positive and 17,506 ER-negative cases, together with 88,937 controls.

Supplementary Table 6. (a) 191 Level 1 predicted target genes. (b) Regions in which target genes are predicted with high confidence

Supplementary Table 7. INQUISIT results for coding/splicing variants.

Supplementary Table 8. INQUISIT results for promoter variants.

Supplementary Table 9. INQUISIT results for distal variants.

Supplementary Table 10. Pathways significantly enriched in CCV and high posterior probability predicted target genes.

Hypergeometric test p-value. P-values adjusted using Benjamini-Hochberg procedure

Supplementary Table 11. BCAC studies ethical agreements

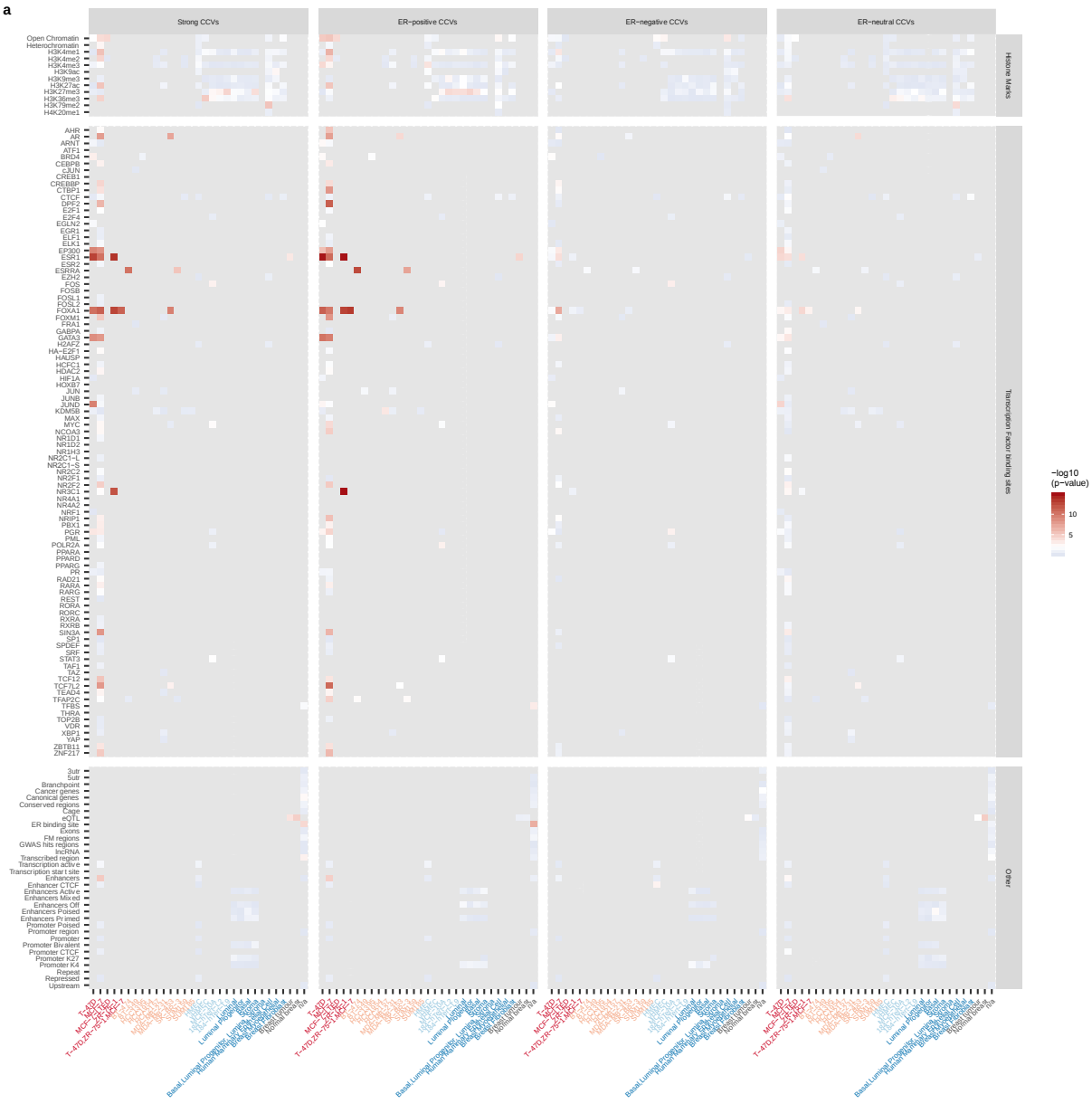
Supplementary Table 12. CIMBA studies ethical agreements

Supplementary Figures

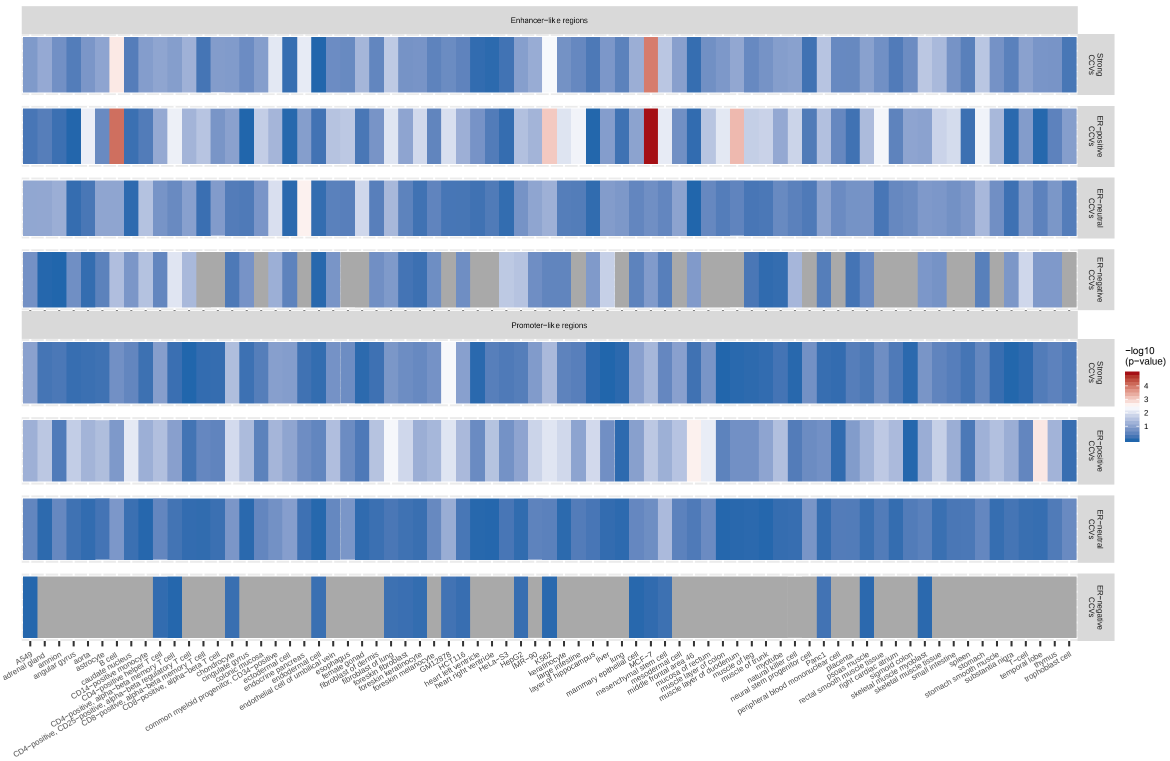
Supplementary Figure 1. Bio-features enrichment

(a) Intersection between CCVs and known bio-features. (b) ENCODE enhancer-like and promoter-like enrichment. ENCODE enhancer-like regions, top, ENCODE promoter like tissues, bottom. Each bar shows the overlap p-value for each subset of CCVs (Strong, ER-positive, ER-negative and ER-neutral) with regulatory regions defined by ENCODE at 73 tissues, primary cells, immortalized cell line, and in vitro differentiated cells (from most significant, dark red, to less significant, blue; grey bars indicate regions where there is <5 CCVs overlapping the region)

Logistic regression robust variance estimation for clustered observations, Wald test X^2 p-values estimated using 67,136 ER-positive and 17,506 ER-negative cases, together with 88,937 controls.

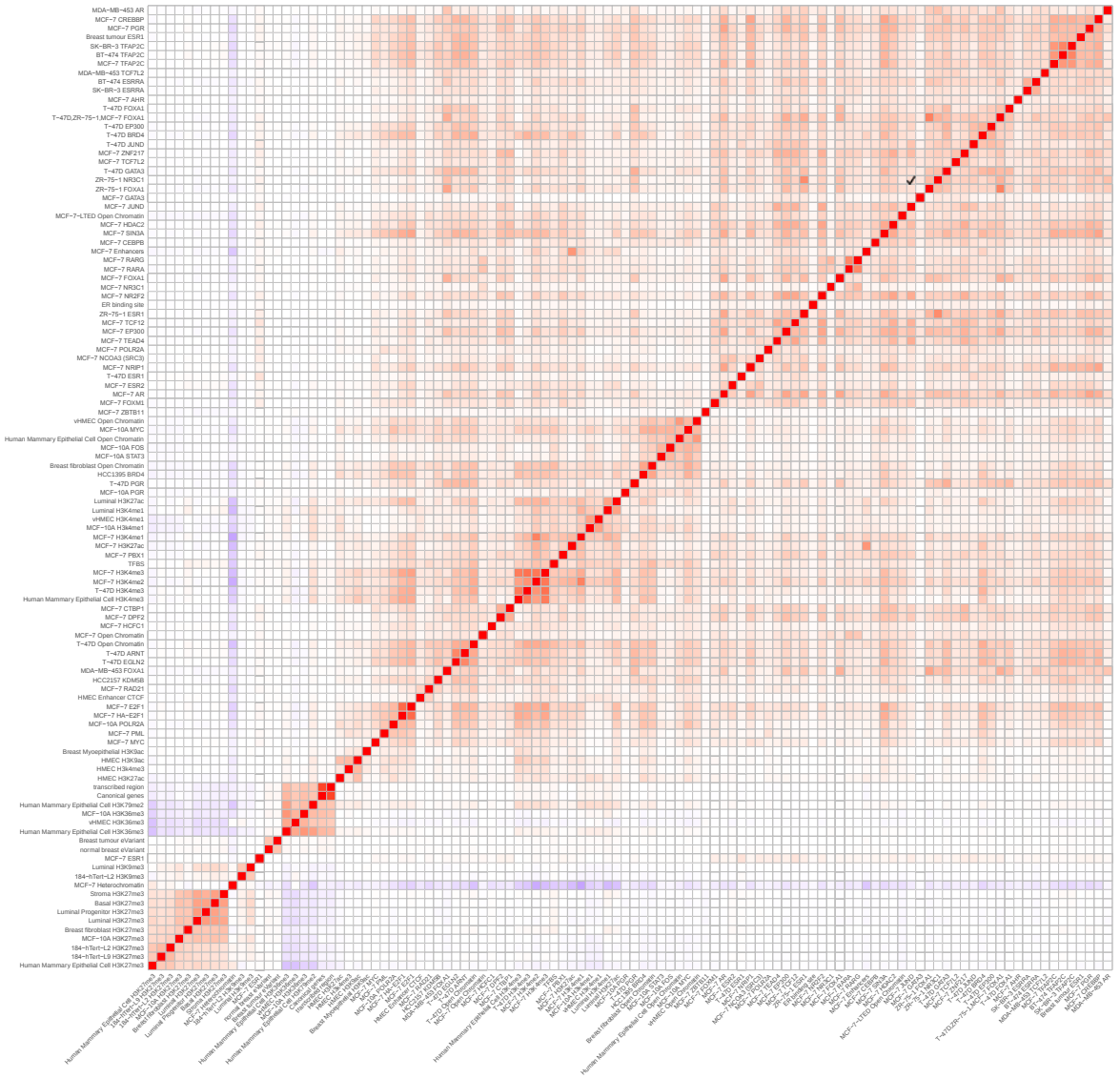

a
Strong CCVs
ER−positive CCVs
ER−negative CCVs
ER−neutral CCVs
Histone Marks
Transcription Factor binding sites
Other
−log10 (p−value)
10
5

b


Enhancer−like regions
Promoter−like regions
Strong CCVs
ER−positive CCVs
ER−neutral CCVs
ER−negative CCVs
−log10 (p−value)
4
3
2
1
A549
adrenal gland
amnion
angular gyrus
aorta
astrocyte
B cell
caudate nucleus
CD14−positive monocyte
CD4−positive helper T cell
CD4−positive, alpha−beta memory T cell
CD4−positive, CD25−positive, alpha−beta regulatory T cell
CD8−positive, alpha−beta memory T cell
CD8−positive, alpha−beta T cell
chondrocyte
cingulate gyrus
colonic mucosa
common myeloid progenitor, CD34−positive
ectodermal cell
endocrine pancreas
endodermal cell
endothelial cell of umbilical vein
esophagus
female gonad
fibroblast of dermis
fibroblast of lung
foreskin fibroblast
foreskin keratinocyte
foreskin melanocyte
GM12878
HCT116
heart left ventricle
heart right ventricle
HeLa−S3
HepG2
IMR−90
K562
keratinocyte
large intestine
layer of hippocampus
liver
lung
mammary epithelial cell
MCF−7
mesenchymal stem cell
mesodermal cell
middle frontal area 46
mucosa of rectum
muscle layer of colon
muscle layer of duodenum
muscle of leg
muscle of trunk
myotube
natural killer cell
neural stem progenitor cell
Panc1
peripheral blood mononuclear cell
placenta
psoas muscle
rectal smooth muscle tissue
right cardiac atrium
sigmoid colon
skeletal muscle myoblast
skeletal muscle tissue
small intestine
spleen
stomach
stomach smooth muscle
substantia nigra
T−cell
temporal lobe
thymus
trophoblast cell

Supplementary Figure 2. Correlation between variants overlapping significantly enriched bio-features

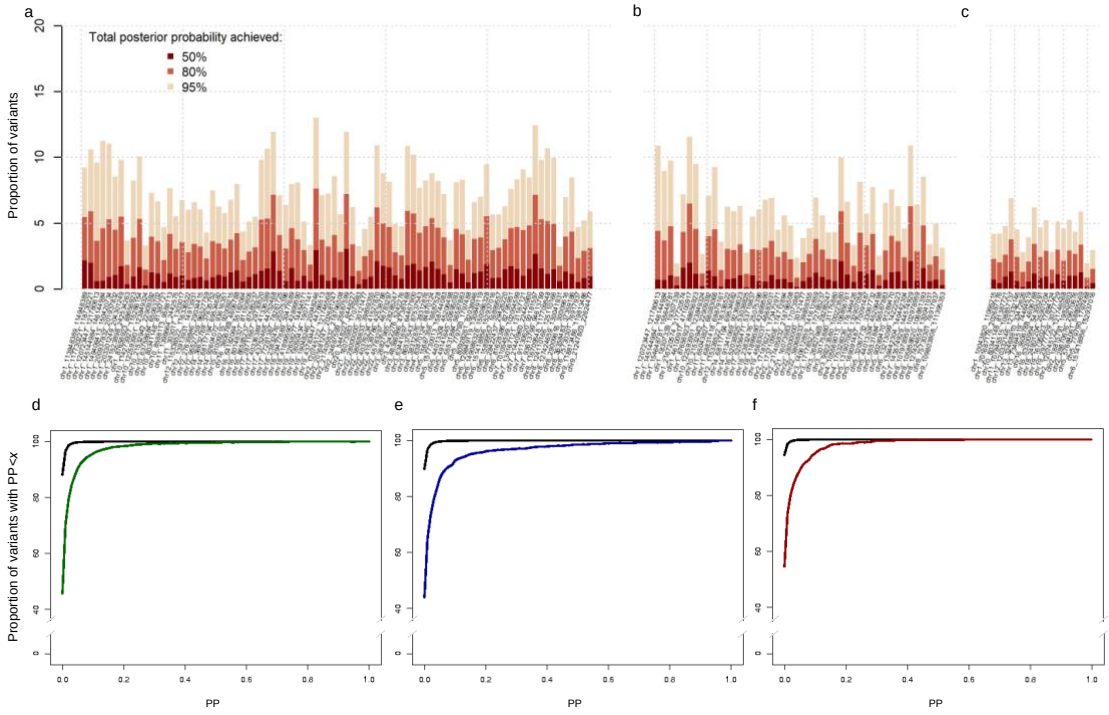
Ranges of Correlation Coefficient values (Pearson's r) estimated using 639,118 variants overlapping enriched biofeatures are denoted by colours as shown in the key labelled: Coeff.



Supplementary Figure 3. Bayesian fine mapping

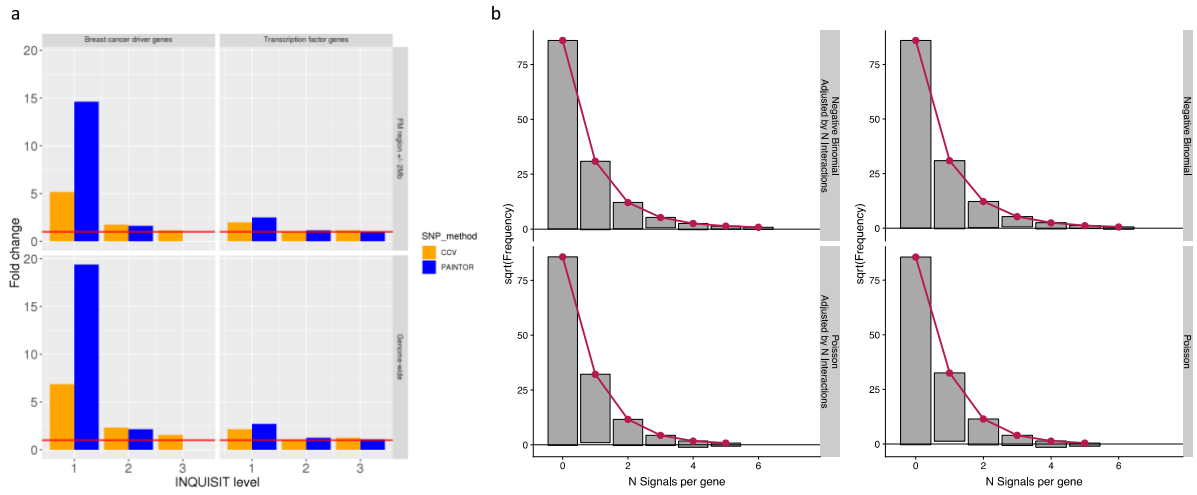
Top: Number of Variants per total posterior probability (PP) from PAINTOR models for (a) ER-all model (b) ER-positive (c) ER-negative.

Bottom: Cumulative distributions of PP for variants in strong signals for overall breast cancer (d, green), strong signals for ER-positive breast cancer (e, blue), and strong signals for ER-negative breast cancer (f, red), compared to cumulative distributions of variants outside of these signals (black).



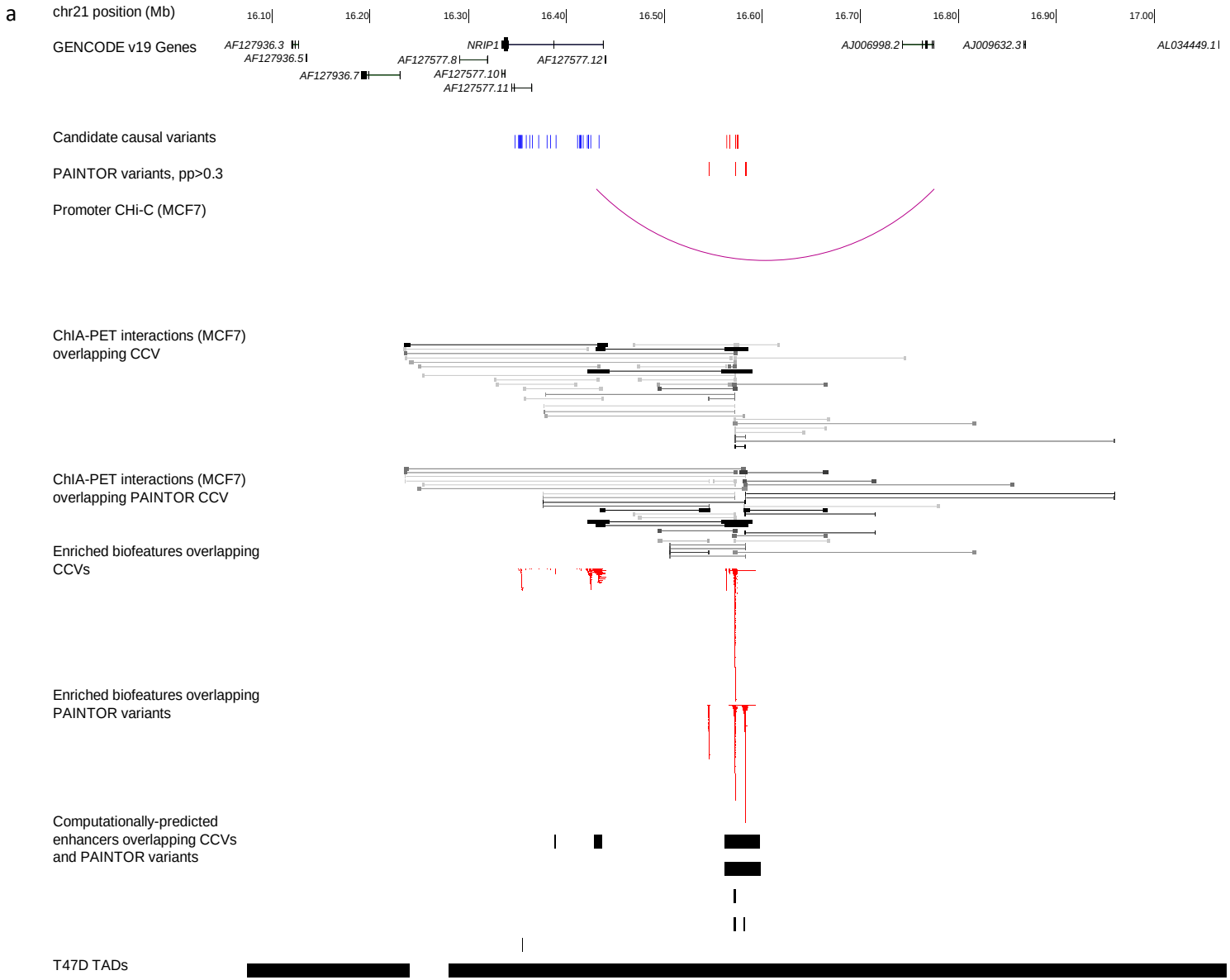
Supplementary Figure 4. Predicted target genes enrichment analysis

(a) Predicted target genes are enriched in known breast cancer driver genes and TFs. (b) Hanging rootograms for the negative binomial model (glm.ng), and the Poisson model (glm.pois). The red line represents the expected counts given the model. The bars denote the observed counts. X-axis shows the count bin. Y-axis shows the square root of the observed or expected count



Supplementary Figure 5. Examples of INQUISIT using genomic features to identify predict target genes.

In each panel, CCVs and PAINTOR variants with posterior probability >0.3 are shown, with independent signals in different colors. Chromatin interactions are shown as arcs (Capture Hi-C from selected breast cell lines) or boxes connected by lines, colored with gray-scale according to interaction score (ENCODE ChIA-PET). Biofeatures which overlap CCVs from the global genomic enrichment analysis are depicted as red boxes. Computationally predicted enhancers including PreSTIGE, FANTOM5 and super-enhancers which overlap risk variants are represented by black boxes. High confidence INQUISIT target gene predictions include *NRIP1* (b), *CHEK2* and *XBP1* (c), and *RPLP0* and *MSI1* (d)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16.20
16.30
16.40
16.50
16.60
16.70
16.80
16.90
17.00
GENCODE v19 Genes
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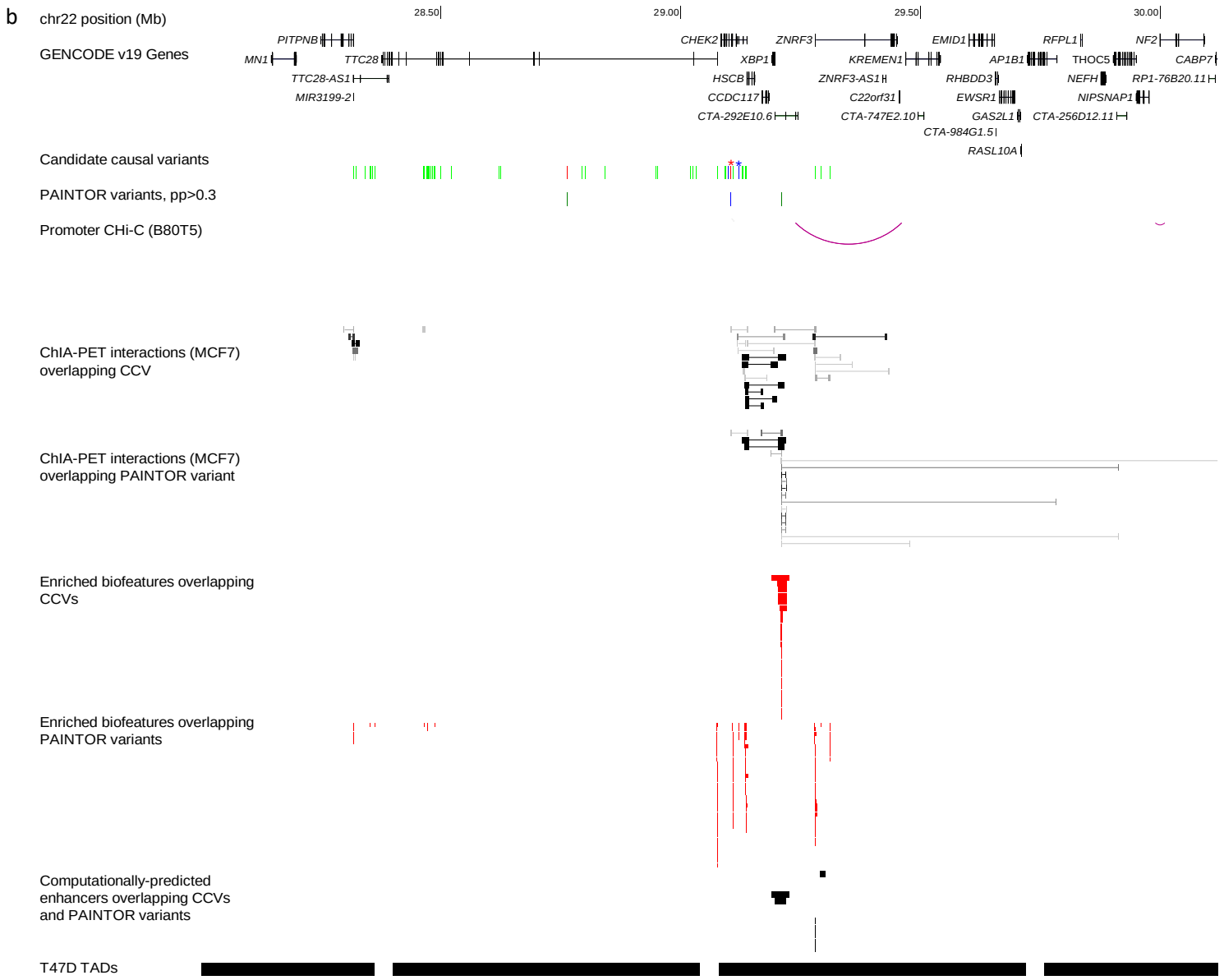
AF127936.5
AF127936.7
NRIP1
AF127577.8
AF127577.10
AF127577.11
AF127577.12
AJ006998.2
AJ009632.3
AL034449.1
Candidate causal variants
PAINTOR variants, pp>0.3
Promoter CHi-C (MCF7)
ChIA-PET interactions (MCF7) overlapping CCV
ChIA-PET interactions (MCF7) overlapping PAINTOR CCV
Enriched biofeatures overlapping CCVs
Enriched biofeatures overlapping PAINTOR variants
Computationally-predicted enhancers overlapping CCVs and PAINTOR variants
T47D TADs


b
chr22 position (Mb)
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29.00
29.50
30.00
GENCODE v19 Genes
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MN1
TTC28
TTC28-AS1
MIR3199-2
CHEK2
XBP1
HSCB
CCDC117
CTA-292E10.6
ZNRF3
ZNRF3-AS1
C22orf31
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KREMEN1
EMID1
RHBDD3
EWSR1
GAS2L1
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RASL10A
AP1B1
RFPL1
THOC5
NEFH
NIPSNAP1
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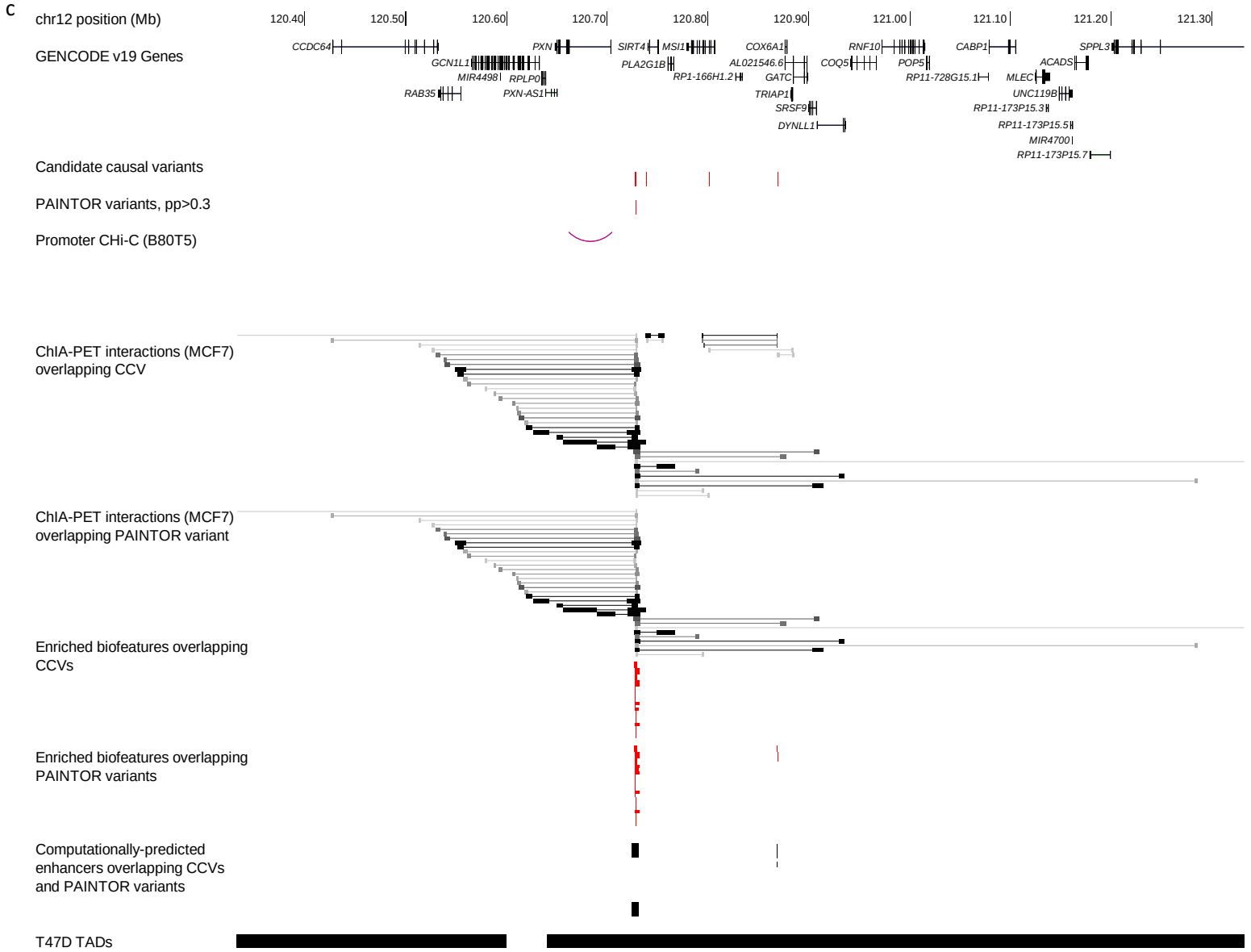
NF2
CABP7
RP1-76B20.11
Candidate causal variants
PAINTOR variants, pp>0.3
Promoter CHi-C (B80T5)
ChIA-PET interactions (MCF7) overlapping CCV
ChIA-PET interactions (MCF7) overlapping PAINTOR variant
Enriched biofeatures overlapping CCVs
Enriched biofeatures overlapping PAINTOR variants
Computationally-predicted enhancers overlapping CCVs and PAINTOR variants
T47D TADs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120.40
120.50
120.60
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120.80
120.90
121.00
121.10
121.20
121.30
GENCODE v19 Genes
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PXN
SIRT4
MSI1
COX6A1
RNF10
CABP1
SPPL3
GCN1L1
PLA2G1B
AL021546.6
COQ5
POP5
ACADS
MIR4498
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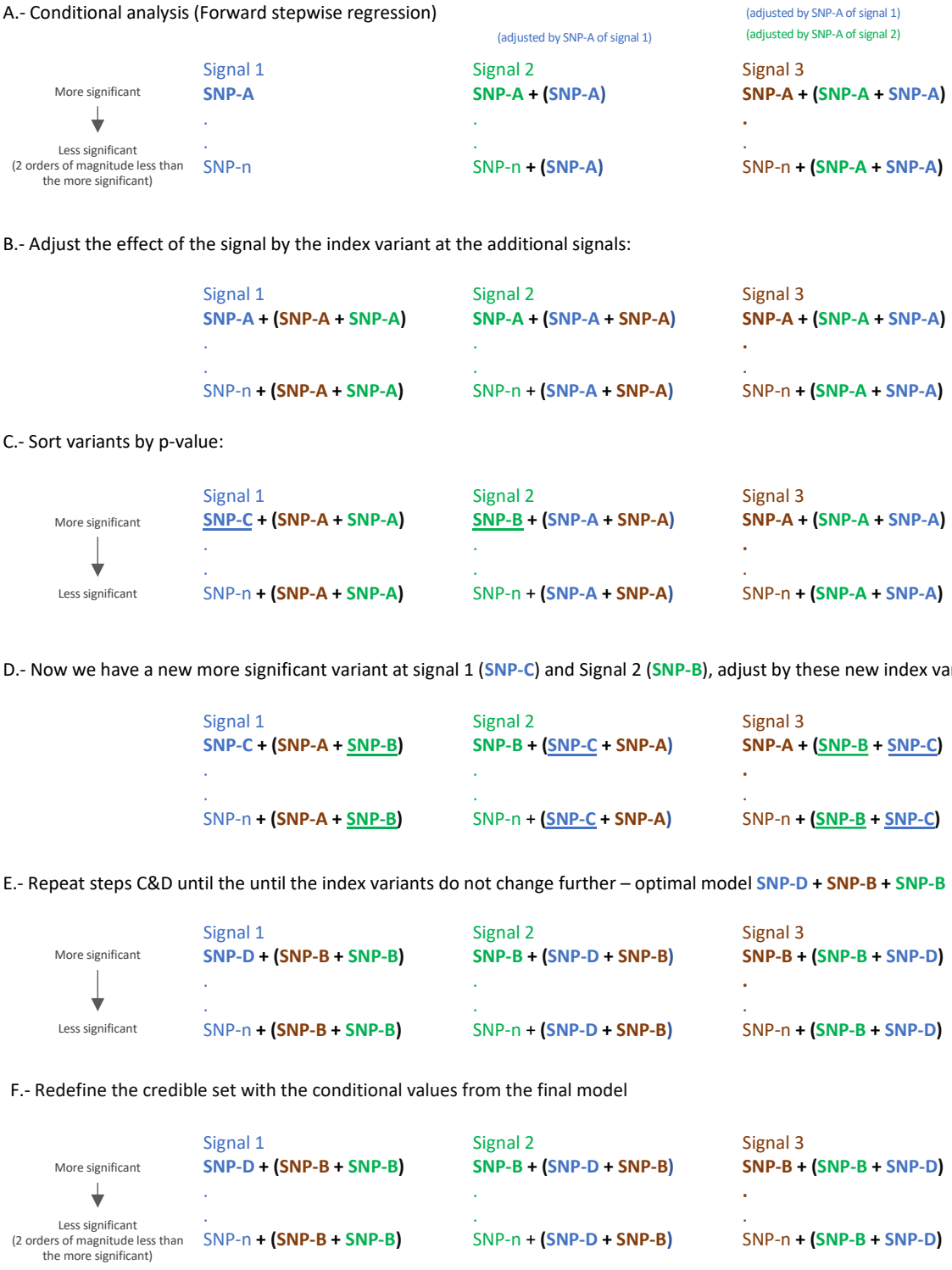
RP1-166H1.2
GATC
RP11-728G15.1
MLEC
RAB35
PXN-AS1
TRIAP1
UNC119B
SRSF9
RP11-173P15.3
DYNLL1
RP11-173P15.5
MIR4700
RP11-173P15.7
Candidate causal variants
PAINTOR variants, pp>0.3
Promoter CHi-C (B80T5)
ChIA-PET interactions (MCF7) overlapping CCV
ChIA-PET interactions (MCF7) overlapping PAINTOR variant
Enriched biofeatures overlapping CCVs
Enriched biofeatures overlapping PAINTOR variants
Computationally-predicted enhancers overlapping CCVs and PAINTOR variants
T47D TADs

Supplementary Figure 6. Selection of a set of credible causal variants

Scheme of the forward stepwise procedure to define a set of credible causal variants



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